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Applicants : Anne Marie Schmidt, et al.
U.S. Serial No: 09/160,649
Filed : October 8, 1998
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inhibits the interaction of a carboxymethyl-lysine-modified advanced glycation endproduct (AGE) with a receptor for advanced glycation end product (RAGE), which comprises:

(a) admixing:

(i) the carboxymethyl-lysine-modified AGE,

(ii) RAGE or a fragment thereof which binds to the carboxymethyl-lysine-modified AGE, and

(iii) the compound;

(b) determining the amount of the AGE bound to the RAGE or the fragment thereof; and

(c) comparing the amount of bound AGE determined in step (b) with the amount determined when the AGE is admixed with RAGE or a fragment thereof in the absence of the compound, thereby determining whether the compound inhibits the interaction of the AGE with RAGE or fragment thereof, wherein a reduction in the amount of binding in the presence of the compound indicates that the compound inhibits the interaction.

24. (Amended) The method of claim 1, wherein the AGE is affixed to a solid surface.

26. (Amended) The method of claim 1, wherein the AGE is detectably labeled.

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Please amend the subject application as follows:

In the claims:

Please amend claim 29 under the provisions of 37 C.F.R. §1.121(c) as follows. A marked up version of amended claim 29 wherein the deleted material is in brackets and the inserted material is underlined is attached hereto as Exhibit A.

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--29. (Amended) The method of claim 1, wherein step (a) occurs
in vitro or in vivo.--

REMARKS

Claims 1, 2, 4-8, 11-13, 15, 17, 18, 20-22, 24-29 and 58-59 are pending in the instant application. Applicants have hereinabove amended claim 29. This amendment does not involve any issue of new matter. Support for this amendment may be found *inter alia* as follows: claim 29: page 9, line 20; claim 58: page 9, lines 23-24. Therefore, entry of this amendment is respectfully requested such that claims 1, 2, 4-8, 11-13, 15, 17, 18, 20-22, 24-29 and 58 will be pending.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 11-12

The Examiner maintained the rejection of claims 11 and 12 under 35 U.S.C. §112, first paragraph, alleging that the specification, while being enabling for a method for determining whether a compound is capable of inhibiting the interaction of a peptide with

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§ 1.121(a) as follows:

On page 9, line 40, please delete "polyepetide" and substitute therefor, --polypeptide--.

In the claims:

Please amend claims 1 and 18 under the provisions of 37 C.F.R. § 1.121(b) by deleting the bracketed word or words and inserting the underlined word or words as follows:

--1. (Amended) A method for determining whether a compound is capable of inhibiting the interaction of a peptide with a receptor for advanced glycation end product (RAGE), which comprises:

(a) admixing:

(i) the peptide, wherein amino groups of the peptide are inactivated by chemical derivitization,

(ii) RAGE or a fragment thereof which is capable of binding the peptide, and

(iii) the compound;

(b) determining the amount of the peptide bound to RAGE or the fragment thereof, and

(c) comparing the amount of bound peptide determined in step (b) with the amount determined when the peptide is admixed with RAGE or a fragment

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What is claimed is:

- 5 1. A method for determining whether a compound is capable of inhibiting the interaction of a peptide with a receptor for advanced glycation end product (RAGE), which comprises:

(a) admixing:

10 (i) the peptide, wherein amino groups of the peptide are inactivated by chemical derivitization,

(ii) RAGE or a fragment thereof, and

(iii) the compound;

(b) determining the amount of the peptide bound to RAGE or the fragment thereof, and

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(c) comparing the amount of bound peptide determined in step (b) with the amount determined when the peptide is admixed with RAGE or a fragment thereof in the absence of the compound, thereby determining whether the compound is capable of inhibiting the interaction of the peptide with RAGE or fragment thereof, wherein a reduction in the amount of binding in the presence of the compound indicates that the compound is capable of inhibiting the interaction.

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2. The method of claim 1, wherein the peptide is an advanced glycation endproduct (AGE) or fragment thereof.

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3. The method of claim 1, wherein the peptide is a carboxymethyl-modified peptide.

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4. The method of claim 1, wherein the peptide is a carboxymethyl-lysine-modified AGE.

5. The method of claim 1, wherein the peptide is a synthetic peptide.

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6. The method of claim 1, wherein the fragment of RAGE is the V-domain.

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7. The method of claim 1, wherein the fragment of RAGE has the amino acid sequence of the V-domain sequence of RAGE.

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8. The method of claim 1, wherein the inactivation by derivitization of the peptide is via chemical modification.

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9. The method of claim 1, wherein the peptide derivative of step (a)(i) comprises an aryl derivative.

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10. The method of claim 9, wherein the aryl derivative comprises a benzoyl derivative.

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11. The method of claim 1, wherein the peptide derivative of step (a)(i) comprises an alkyl derivative.

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12. The method of claim 11, wherein the alkyl derivative comprises an acetyl derivative, a propyl derivative, an isopropyl derivative, a butyl derivative, an isobutyl derivative, or a carboxymethyl derivative.

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13. The method of claim 1, wherein the RAGE or fragment

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thereof of step (a)(ii) is synthetic.

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14. The compound of claim 1, wherein the compound has a net negative charge or a net positive charge.

15. The method of claim 1, wherein the compound comprises a fragment of naturally occurring soluble receptor for advanced glycation endproduct (sRAGE).

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16. The method of claim 1, wherein the compound is a peptidomimetic.

17. The method of claim 1, wherein the compound is an organic molecule.

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18. The method of claim 1, wherein the compound is a polypeptide, a nucleic acid, or an inorganic chemical.

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19. The method of claim 1, wherein the compound is a molecule of less than 10,000 daltons.

20. The method of claim 1, wherein the compound is an antibody or a fragment thereof.

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21. The method of claim 20, wherein the antibody is a polyclonal or monoclonal antibody.

22. The method of claim 20, wherein the antibody is humanized, chimeric or primatized.

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23. The method of claim 1, wherein the compound is a mutated AGE or fragment thereof or a mutated RAGE or a fragment thereof.

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24. The method of claim 1, wherein the peptide is affixed

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to a solid surface.

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25. The method of claim 1, wherein the RAGE or the fragment thereof is affixed to a solid surface.

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26. The method of claim 1, wherein the peptide is detectably labeled.

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27. The method of claim 1, wherein the RAGE or the fragment thereof is detectably labeled.

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28. The method of claim 26 or 27, wherein the detectable label comprises fluorescence, biotin, or radioactivity.

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29. The method of claim 1, wherein step (a) occurs in a cell.

30. The method of claim 1, wherein step (a) occurs in an animal.

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31. The method of claim 30, wherein the animal is a transgenic animal which overexpresses RAGE or a transgenic animal which does not express RAGE.

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32. A method for inhibiting the interaction of an advanced glycation endproduct (AGE) with a receptor for advanced glycation endproduct (RAGE) in a subject which comprises administering to the subject an amount of a compound effective to inhibit the interaction between the AGE and the RAGE in the subject.

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33. The method of claim 32, wherein the subject is a human, a primate, a mouse, a rat or a dog.

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34. The method of claim 32, wherein the administration

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comprises intralesional, intraperitoneal, intramuscular or intravenous injection; infusion; liposome-mediated delivery; or topical, nasal, oral, ocular or otic delivery.

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35. The method of claim 32, wherein the compound is administered hourly, daily, weekly, monthly or annually.

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36. The method of claim 32, wherein the effective amount of the compound comprises from about 0.000001 mg/kg body weight to about 100 mg/kg body weight.

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37. The method of claim 32, wherein the subject is suffering from kidney failure.

38. The method of claim 32, wherein the subject is suffering from diabetes.

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39. The method of claim 32, wherein the subject is suffering from systemic lupus erythematosus or inflammatory lupus nephritis.

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40. The method of claim 32, wherein the subject is an obese subject.

41. The method of claim 32, wherein the subject is an aged subject.

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42. The method of claim 32, wherein the subject is suffering from amyloidoses.

43. The method of claim 32, wherein the subject is suffering from inflammation.

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44. The method of claim 32, further comprising administering to the subject a pharmaceutically acceptable carrier during the administration of the compound.
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45. The method of claim 44, wherein the carrier comprises a diluent.
46. The method of claim 44, wherein the carrier comprises, a virus, a liposome, a microencapsule, a polymer encapsulated cell or a retroviral vector.
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47. The method of claim 44, wherein the carrier is an aerosol, intravenous, oral or topical carrier.
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- 10/01/01 48. The method of claim 44, wherein the compound is administered from a time release implant.
49. A method for inhibiting the interaction of an advanced glycation endproduct (AGE) with a receptor for advanced glycation endproduct (RAGE) in a subject which comprises administering to the subject an amount of quinine or a derivative thereof effective to inhibit the interaction between AGE and RAGE in subject.
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50. The method of claim 49, wherein the derivative has a different chemical structure than quinine and the derivative has the same overall charge as quinine.
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51. A method for inhibiting the interaction of an advanced glycation endproduct (AGE) with a receptor for advanced glycation endproduct (RAGE) in a subject which comprises administering to the subject an amount of quinidine or a derivative thereof effective to inhibit the interaction between AGE and RAGE in subject.
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52. The method of claim 51, wherein the derivative has a different chemical structure than quinidine and the derivative has the same overall charge as quinidine.
- 5 53. A compound identified by the method of claim 1, useful for the treatment of diabetes in a subject.
- 10/01/01 54. A compound identified by the method of claim 1, useful for the treatment of systemic lupus erythematosus or inflammatory lupus nephritis in a subject.
- 10 55. A compound identified by the method of claim 1, useful for the treatment of amyloidoses in a subject.
- 15 56. A compound identified by the method of claim 1, useful for the treatment of inflammation in a subject.
57. A previously unknown compound identified by the method of claim 1.

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What is claimed is:

allowed

Claims

(not & so out)

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1. (Twice Amended) A method for determining whether a compound inhibits the interaction of a carboxymethyl-lysine-modified advanced glycation endproduct (AGE) with a receptor for advanced glycation end product (RAGE), which comprises:
 - (a) admixing:
 - (i) the carboxymethyl-lysine-modified AGE,
 - (ii) RAGE or a fragment thereof which binds to the carboxymethyl-lysine-modified AGE, and
 - (iii) the compound;
 - (b) determining the amount of the AGE bound to the RAGE or the fragment thereof; and
 - (c) comparing the amount of bound AGE determined in step (b) with the amount determined when the AGE is admixed with RAGE or a fragment thereof in the absence of the compound, thereby determining whether the compound inhibits the interaction of the AGE with RAGE or fragment thereof, wherein a reduction in the amount of binding in the presence of the compound indicates that the compound inhibits the interaction.

10 6. The method of claim 1, wherein the fragment of RAGE is the V-domain.

15 7. The method of claim 1, wherein the fragment of RAGE has the amino acid sequence of the V-domain sequence of RAGE.

35 13. The method of claim 1, wherein the RAGE or fragment thereof of step (a)(ii) is synthetic.

15 15. The method of claim 1, wherein the compound comprises a fragment of naturally occurring soluble receptor for advanced glycation endproduct (sRAGE).

17. The method of claim 1, wherein the compound is an organic molecule.

18. (Amended) The method of claim 1, wherein the compound is a [polyepetide] polypeptide, a nucleic acid, or an inorganic chemical.--

20. The method of claim 1, wherein the compound is an antibody or a fragment thereof.

25 21. The method of claim 20, wherein the antibody is a polyclonal or monoclonal antibody.

22. The method of claim 20, wherein the antibody is humanized, chimeric or primatized.

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24. (Amended) The method of claim 1, wherein the AGE is affixed to a solid surface.

25. The method of claim 1, wherein the RAGE or the fragment thereof is affixed to a solid surface.

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26. (Amended) The method of claim 1, wherein the AGE is detectably labeled.

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27. The method of claim 1, wherein the RAGE or the fragment thereof is detectably labeled.

28. The method of claim 26 or 27, wherein the detectable label comprises fluorescence, biotin, or radioactivity.

~~29. (Amended) The method of claim 1, wherein step (a) occurs in vitro or in vivo.~~